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REVIEW

Cefditoren: a clinical overview

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SUMMARY

Cefditoren is an oral third-generation cephalosporin with a large spectrum activity against Gram-negative and Gram-positive bacteria which are reported to be responsible for respiratory tract and skin and skin structure infections. In this work we reviewed the pharmacodynamics, pharmacokinetics, and the main clinical indications of cefditoren. Similarly to other beta-lactams, cefditoren is a time-dependent antibiotic, and its "best" PK/PD target is probably 40% dosing interval time > 4- 5-fold MIC and 40-70% dosing interval time > 4- 5-fold MIC for bacteriostatic and bactericidal effect, respectively. In fasting patients oral bioavailability is low and increases when the drug is taken with food. This cephalosporin has significant bactericidal activity against *S. pneumoniae* (both penicillin-susceptible and penicillin-resistant strains), *S. pyogenes, H. Influenzae* and *M. catarrhalis*, as well as methicillin-susceptible *S. aureus* (MSSA). Regarding *Enterobacterales*, cefditoren has very low $MICs_{90}$ against *K. pneumoniae* and*E. coli* but is not active against AmpC-, ESBL- and carbapenemase-producer' strains. Licensed indications are treatment of exacerbations of chronic bronchitis,acute rhinosinusitis, otitis media, upper respiratory tract infections (pharyngitis/tonsillitis), lower community-acquired respiratory tract infections (LRTIs), and skin and skin-structure infections (SSTI). Cefditoren might have a role in switching from parenteral to oral therapy in acute pyelonephritis and LRTIs. with a reduction of adverse effects and hospital costs. Eventually, due to its supposed binding to enterococcal penicillin binding proteins (PBPs) cefditoren, in combination with other beta-lactams, might have a role in partial oral enterococcal endocarditis treatment..

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INTRODUCTION

Cefditoren is an oral third-generation cephalosporin with a large spectrum of activity against Gram-negative and Gram-positive bacteria that are able to cause respiratory tract and skin and skin structure infections. This is due to the high affinity of cefditoren to the Penicillin Binding Proteins (PBPs) of all those microorganisms. PBPs are located in the cytoplasmic membrane of bacteria and are involved in the continuous modelling and growth of peptidoglycan (Sauvage *et al.*, 2008).
Cefditoren has shown efficacy against major aetiologic agents of community acquired respiratory infections (CAP) (*S. pneumoniae, M. catarrhalis, H. Influenzae*), as well as *Enterobacterales* and non-enteric Gram-negative bacilli, staphylococci and other aerobic and anaerobic Gram-positive cocci, β-haemolytic and viridans streptococci. Enterococci, *Pseudomonas aeruginosa* and most Gram-negative anaerobes are not susceptible at the concentration reached in human tissues (Jones *et al.* 2001).
This review addresses the pharmacodynamics, pharmacokinetics, and main clinical indications of ceftibuten.

Key words:
Cefditoren, Clinical indications, Pharmacodynamic, Pharmacokinetics.

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PHARMACODYNAMIC AND PHARMACOKINETIC OF CEFDITOREN

Similar to other beta-lactams, cefditoren is a time-dependent antibiotic. Studies have shown that in order to achieve microbiological and clinical cure, free cephalosporin concentrations should be 4-5 times higher than the minimal inhibitory concentration (MIC) for at least 40-70% of the dosing time (T) (Mouton *et al.*, 2007; Li *et al.*, 2007) Therefore the "best" cefditoren PK/PD index is probably 40-70% T>4-5 times MIC (Mazzei *et al.*, 2004). Beta-lactams are known to alter bacterial cell structure by covalently binding to PBPs. PBPs are located in the cytoplasmic membrane of bacteria and are in-

volved in the continuous modelling and growth of peptidoglycan. By binding to PBPs, cefditoren turns them off, and its post-antibiotic effect may reflect the time required by the microorganisms to synthesise new enzymes (Zhanel *et al.*, 1991; Sauvage *et al.*, 2008). Indeed, unlike other cephalosporins, cefditoren pivoxil has been shown to have a long-lasting post-antibiotic effect. This was demonstrated *in vitro* and *in vivo* for both Gram-positive and Gram-negative bacteria, except for *P. aeruginosa* (Mazzei *et al.*, 2004). In particular, it has a post-antibiotic effect at concentrations 4 x MIC between 1 and 2.5 hours against *S. pyogenes, S. pneumoniae* (also resistant to penicillin), *S. aureus* and *M. catarrhalis* (Mazzei *et al.*, 2004).

The pharmacokinetic characteristics of cefditoren, administered orally as cefditoren pivoxil, were evaluated in healthy volunteers and in patients undergoing bronchoscopy or with renal or hepatic insufficiency. After oral assumption of 200 mg or 400 mg, the drug is hydrolysed by esterases of the intestinal wall and then completely absorbed. Bioavailability is 15-20% in fasting patients, but maximum plasma concentration and area under the concentration time curve (AUC) increase up to 50 and 70%, respectively, when the drug is taken along with a fatty meal (Mazzei *et al.*, 2004; Wellington *et al.*, 2004). Absorption time of a single dose of 200 mg and 400 mg ranges from 1.5 to 3 hours, with peak concentrations of 2.7 - 3.1 mg/l and 3.8 - 4.6 mg/lL, respectively. After absorption, blood concentrations are maintained above 0.5 - 1 mg/l for 4-6 hours (Mazzei *et al.*, 2004; Wellington *et al.*, 2004). At the 12-hourly administered dose tested for 7 days, no accumulation was seen (Mazzei *et al.*, 2004; Wellington *et al.*, 2004). Cefditoren is approximately 88% bound to plasma proteins, and the volume of distribution averages 9.3 l at steady state (Mazzei *et al.*, 2004; Wellington *et al.*, 2004). In lung parenchyma, bronchial mucosa and tonsillar tissue show concentrations higher than the MIC_{90} of the most common respiratory pathogens, with a tissue/plasma ratio of 32/55% (Mazzei *et al.*, 2004). The cephem derivative does not undergo metabolism and is mainly eliminated by the kidney, with a clearance of 68/93 ml/min in healthy volunteers. In case of moderate (ClCr 30-50 ml/min) or severe (ClCr <30 ml/min) renal insufficiency, there is a 1.5/3-fold increase in peak blood values and AUC. However, no dosage adjustment is necessary at the 200 mg dose (Mazzei *et al.*, 2004). Dosing regimens also do not require adjustment for mild or moderate hepatic impairment (Child-Pugh class A and B) (Mazzei *et al.*, 2004; Wellington *et al.*, 2004). Differences in gender and age are not clinically relevant and do not require adjustments of the therapeutic dose (Mazzei *et al.*, 2004). No data are available regarding penetration of cefditoren into skin and soft tissues. However, we can assume that cefditoren behaves like other beta-lactams, which are reported to have good skin and soft tissue penetration and activity (Gainer 2nd, 1991; Hedström, 1984).

TIME KILL STUDY

In a time kill study cefditoren was the only antibiotic (compared with amoxicillin-clavulanate and levofloxacin) showing significant bactericidal activity against penicillin-susceptible (PEN-S) and resistant (PEN-R) *S. pneumoniae* strains, *S. pyogenes* and *M. catarrhalis* (Mezzatesta *et al.,* 2010). It also exhibited a bactericidal effect against methicillin-susceptible *Staphylococcus aureus* (MSSA) (Mezzatesta *et al.,* 2010). Furthermore, cefditoren was as effective as fluoroquinolone and more effective than other cephalosporins against β-lactamase-producing strains of *H. Influenzae* (Mezzatesta *et al.,* 2010).

CEFDITOREN ACTIVITY AGAINST PBP OF *S. PNEUMONIAE*

Cefditoren, like all beta-lactams, interacts with pathogen penicillin-binding proteins (PBPs). PBPs are membrane enzymes that play a crucial role in synthesis of the peptidoglycan of the bacterial cell membrane. Specifically, *S. pneumoniae* has six PBPs: the high molecular weight (HMW) class A PBP 1A, 1B and 2A; the HMW class B PBP 2B and 2X; and low molecular weight PBP3. Cefditoren has excellent affinity for PBP2X, and this explains its remarkable efficacy against *S. pneumoniae*. Indeed, it has been demonstrated that in the PBP2X-cefditoren complex the methylthiazole group of the C-3 side chain of cefditoren interacts with an additional hydrophobic pocket that is formed by a change in the conformation of Trp374. In addition, the C-7 side chain of cefditoren is stabilised by hydrogen bonds and hydrophobic interactions with the active site, where a conformational change occurs upon binding (Yamada *et al.,* 2008).

COMPARISON OF SENSITIVITY WITH OTHER ANTIBIOTIC CLASSES

The activity of cefditoren against *S. pneumoniae* is superior to all commercially available cephalosporins and at least equal to amoxicillin-clavulanate. As opposed to cefixime and ceftibuten, cefditoren is active against methicillin-susceptible staphylococci with the same effectiveness as cefuroxime, cefaclor and cefprozil (Jones *et al.,* 2001).

Microbiological data collected in Italy from January to September 2009 showed that cefditoren had the lowest MIC_{90} against 965 strains of *S. pneumoniae*, followed by cefotaxime and ceftriaxone. Against 470 *H. Influenzae* strains (regardless of their resistance

to β-lactams), cefditoren was the oral cephalosporin with the best *in vitro* activity, with efficacy comparable to injectable cephalosporins and levofloxacin. *S. pyogenes* was also sensitive to all β-lactams antibiotics including cefditoren (Tempera e*t al.,* 2010). *M. catarrhalis* (sensitive to β-lactams) had reduced susceptibility only to cefuroxime and macrolides. Cefditoren, cefotaxime, and ceftriaxone showed the lowest MIC_{50} and MIC_{90} in non ESBL-producer strains (Tempera *et al.,* 2010). With regard to *Enterobacterales*, cefditoren and levofloxacin had the lowest MIC_{90} against *K. pneumoniae*; cefditoren and third generation injectable cephalosporin had the lowest MIC_{90} against *E. coli*, while levofloxacin was less active (Tempera *et al.,* 2010). Cefditoren was not active against ESBL- and carbapenemases-producer strains.

Another longitudinal study evaluating the activity of cefditoren and other antibiotics against PEN-R *S. pneumoniae* strains in the period 2004-2020 demonstrated that the antibiotic with the lowest proportion of resistance was cefditoren (<0.4%), followed by cefotaxime (<5%), penicillin (<6.5%) and levofloxacin (<7%). Cefixime was the cephalosporin with the highest MIC_{90} (32 mg/L) and MIC_{50} (8-16 mg/L), followed by cefpodoxime (MIC_{90} 4 mg/l and MIC_{50} 2 mg/l). Cefditoren MIC_{90} and MIC_{50} were 1 mg/L and 0.25-0.5 mg/L, respectively (Sempere *et al.,* 2022).

MECHANISMS OF RESISTANCE

The production of beta-lactamase is one of the most frequent mechanisms of resistance to beta-lactams. This resistance is due to the fact that the enzyme of the causative agent (plasmid or chromosomal) is able to hydrolyse the amide bond of the beta lactam. Concerning *H. influenzae,* plasmidic TEM-1 beta-lactamase is the most frequent mechanism of resistance, followed by the production of ROB-1, another plasmid-harboured beta-lactamase (Wellington *et al.,* 2004; Hasegawa *et al.,* 2003). Regarding *M. catarrhalis*, mechanisms of resistance are linked to the production of chromosomal beta-lactamases such as BRO-1, BRO-2, and BRO-3. Cefditoren has the capacity to resist hydrolysis by many plasmidic beta-lactamases, in particular TEM-1, ROB-1, SHV-1, SHV-3, SHV-10, OXA-5, OXA-12, PSE-1, PSE-2, PSE-3, PSE-4, SAR-1, HMS-1, CARB-4, LCR-1, TLE-1, and OHIO-1. On the contrary, it is susceptible to hydrolysis by other plasmidic extended-spectrum beta lactamases such as TEM-3, TEM-4, TEM-5, TOHO-1, SHV2- SHV-7, SHV-9, SHV-12, and PER-1 (Wellington *et al.,* 2004; Ehrhardt *et al.,* 2000). *In vitro* studies demonstrated that cefditoren is not a good substrate for beta lactamases produced by *H. influenzae* (including TEM-1 and ROB-1) and *M. catarrhalis* (Wellington *et al.,* 2004; Hasegawa *et al.,* 2003). Cefditoren has been found to remain effective against ampicillin-resistant beta-lactamase negative (BLNAR) *H. influenzae* whose beta-lactam resistance is mediated by modifications of PBP3a and/or PBP3b (Wellington *et al.,* 2004; Ehrhardt *et al.,* 2000; Hasegawa *et al.,* 2003). Alterations of PBPs are the main determinants of resistance to beta-lactams in *S. pneumoniae* and *S.aureus*. Cefditoren retains good antibacterial activity against *S. pneumoniae* despite amino acid alterations in PBP1a, PBP2x, and PBP2b. (Wellington *et al.,* 2004)

INDICATIONS

I. Cefditoren in the treatment of acute rhinosinusitis

The microorganisms most often implicated in community-acquired acute rhinosinusitis in patients without significant comorbidity are *S. pneumoniae*, *H. influenzae,* and *M. catarrhalis*. Four classes of antibiotics are reported to be active against these three microorganisms: penicillins, cephalosporins, fluoroquinolones, and macrolides. When selecting the most appropriate antibiotic for empirical therapy,

Table 1 - *Empirical antimicrobial treatment regimen (Barberan et al. 2008).*

	1st choice	*Alternatives*	*Duration (days)*
Mild maxillary rhinosinusitis in patient who has not received antibiotic treatment in the last 3 months	- Symptomatic treatment or amoxicillin-clavulanic acid - Cefditoren	- Macrolide	5-7
Mild or moderate maxillary rhinosinusitis with antibiotic treatment in the last 3 months and/or frontal sinusitis or sphenoid involvement	- Levofloxacin - Moxifloxacin	- Amoxicillin-clavulanic acid - Cefditoren	7-10
Severe (or complicated) rhinosinusitis	- Ceftriaxone - Cefotaxime - Amoxicillin-clavulanic acid	- Ertapenem	≥10
Maxillary sinusitis of dental origin and/or chronic sinusitis	- Amoxicillin-clavulanic acid - Moxifloxacin		≥10

anti-pneumococcal activity is a fundamental element to take into account, since *S. pneumoniae* is the most common aetiologic agent and pneumococcal rhinosinusitis shows a lower tendency to spontaneous resolution and a higher incidence of complications, including hospitalisation (Antimicrobial treatment guidelines for acute rhinosinusitis, 2000). Maxillary rhinosinusitis of odontogenic origin and chronic forms of rhinosinusitis often involve a polymicrobial flora including oral anaerobic microorganisms (Brook *et al*., 2005). Cephalosporins that show good activity against *S. pneumoniae* and *H. influenzae* are cefuroxime, cefpodoxime and cefditoren (*Table 1*). Of these, cefditoren is the most bactericidal and the most active *in vitro*, with MIC_{90} values similar to those of third-generation parenteral cephalosporins such as cefotaxime and ceftriaxone, 2 to 4 times lower than those of cefpodoxime, and 8 to 16 times lower than those of cefuroxime (Soriano *et al*., 2003; Barberan *et al*., 2008).

II. Cefditoren in the treatment of otitis media in children

Otitis media (OM) is one of the most common infections in children (Arguedas *et al*., 1998; Ulloa *et al.,* 2014). More than 80% of children develop at least one OM episode before 3 years of age and around 40% have six or more episodes by the age of 7 (Vergison *et al*., 2010). In this population the four most common pathogens causing OM are *S. pneumoniae, H. influenzae, M. catarrhalis*, and *S. pyogenes*. The optimal agent should be active against these pathogens and stable in the presence of β-lactamase (Arguedas *et al*., 1991). For *S. pneumoniae*, cefditoren activity was similar to that of the cephalosporins commonly used for the treatment of OM, but cefditoren was more active than penicillin, erythromycin, and clarithromycin. For PEN-R *S. pneumoniae*, cefditoren showed very good activity, with only 7% of the strains being resistant. Cefditoren was found to be the drug with the lowest MIC values against multi-drug resistant (≥ three antibiotic classes among penicillins, cephalosporins, macrolides, fluoroquinolones) *S. pneumoniae* strains (Ulloa *et al.,* 2014). Cefditoren also maintained the same level of activity against *H. influenzae* regardless of the production of β-lactamases or ampicillin resistance. The production of β-lactamase by *H. influenzae* and *M. catarrhalis* did not influence the activity of cefditoren, and *S. pyogenes* was susceptible to all β-lactams studied, including cefditoren, with a low resistance rate to macrolides. These findings suggest that cefditoren might be one of the agents of choice for empirical therapy of OM (Arguedas *et al*., 1991; Ulloa *et al.,* 2014).

III. Cefditoren in the treatment of upper respiratory tract infections (pharyngitis/tonsillitis)

Upper respiratory tract infections are one of the major causes of clinical examinations in an ambulatory care setting. *S. pyogenes, S. pneumoniae,* and *H. influenzae* are the most prevalent isolates in community-acquired upper respiratory tract infections. In the pooled analysis, clinical outcomes with cefditoren were similar to comparators (standard oral treatments with cefuroxime or amoxicillin/clavulanate) (Granizzo *et al*., 2008; Desrosiers *et al*., 2006).

IV. Cefditoren in the treatment of exacerbations of chronic bronchitis and community-acquired lower respiratory tract infections

Clinical studies have documented the efficacy of cefditoren in the treatment of community-acquired lower respiratory tract infections (LRTIs), such as acute exacerbations of chronic bronchitis (AECB) and mild-to-moderate community-acquired pneumonia (CAP), due to its activity on the microorganisms most implicated in these diseases (Blasi *et al*., 2010). The activity spectrum of cefditoren against Gram-positive and Gram-negative bacteria includes common respiratory pathogens such as *S. pneumoniae*, *H. influenzae, M. catarrhalis, S. pyogenes, K. pneumoniae,* and MSSA (Di Marco *et al.,* 2014; Clark *et al.,* 2002). Biedenbach and colleagues demonstrated that cefditoren was active against several isolates of PEN-S *S. pneumoniae* isolates, with MIC_{90} ≤0.03 mg/l (Tempera *et al*., 2010); it also proved to be one of the most potent orally-administered cephalosporins against this organism due to PBP2X binding (Biedenbach *et al.,* 2009; Cantòn *et al*., 2009). Cefditoren was the most active oral cephem tested against beta-lactamase-producing and BLNAR *Haemophilus influenzae*, with MIC_{90} < or = 0.03 microg/mL and >99% (Biedenbach *et al.,* 2009; Tempera *et al*., 2010). *Moraxella catarrhalis* cefditoren MIC_{90} of 0.5 microg/ml was higher but still close to that of amoxicillin/clavulanate and cefdinir. MSSA MIC_{90} is 1 mg/l (*Figure 1*). Moreover, cefditoren proved to be 100% active against beta-haemolytic streptococci (Biedenbach *et al*., 2009; Tempera *et al*., 2010).

Regarding dosing, results of studies carried out on cefditoren-pivoxil at the dose of 200 mg 12-hourly demonstrated concentrations above the MIC for a sufficiently long period of time to ensure clinical and microbiological efficacy (Blasi *et al*., 2010; Mazzei *et al*., 2004). Another recent study analysed the effect of cefditoren (200 mg twice daily for 5 days) against the comparator (levofloxacin 500 mg once daily for 7 days) in mild to moderate acute exacerbation of chronic obstructive pulmonary disease (COPD) and tested the effect on reduction of serum inflammatory biomarkers, clinical efficacy, and microbiological eradication. No significant differences in clinical and microbiological cure were found, but a significant reduction of IL-6 and KL-6 (two mediators of lung inflammation and epithelial damage) was demonstrated, hence the authors concluded that cefditor-

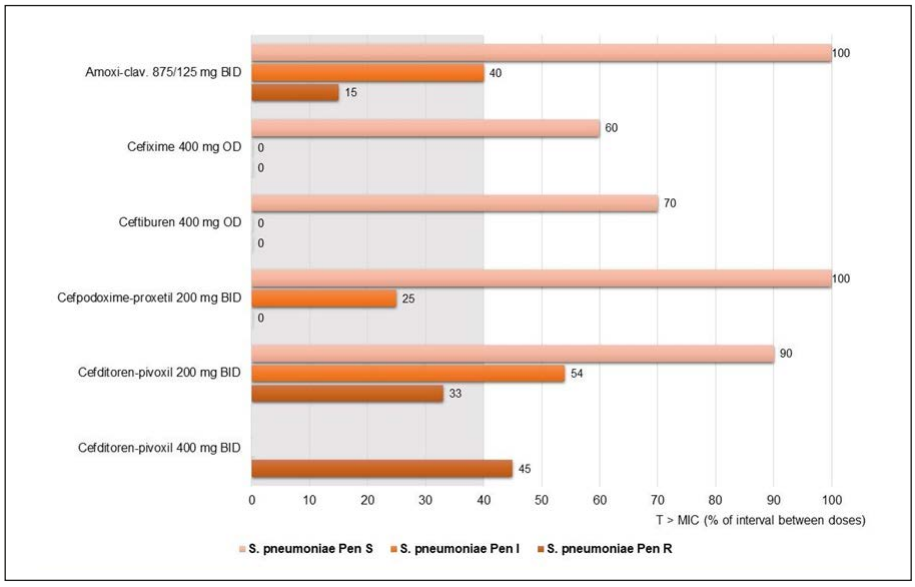

Figure 1 - *Antibiotics blood concentration time (%) above MIC90 (T> MIC) in S. pneumoniae (Di Marco et al. 2014; Blasi et al. 2010).*
Legend: BID – two times a day; I – Intermediate; OD – once a day; Pen – Penicillin; R – Resistant; S – Sensitive.

en might represents a valid option in the treatment of mild to moderately severe cases of exacerbation of chronic bronchitis in the outpatient care setting (Blasi *et al.*, 2013) (*Table 2*).
Recent data on the *in vitro* activity of several antibiotics on major respiratory pathogens isolated in Italy are presented in two studies conducted in 2007 and 2009. The results are as follows:

1) PEN-R *S. pneumoniae* strains also exhibit high levels of resistance against all oral cephalosporins (100% to cefaclor). In the absence of breakpoints, it is difficult to compare the efficacy of different antibiotics but, considering the MIC_{90} and the pharmacokinetic features of ceftibuten and cefixime, cefditoren turned out to be the only antibiotic consistently active on all strains of *S. pneumoniae*, followed by the injectable cephalosporins cefotaxime and ceftriaxone (Blasi *et al.*, 2010).
2) In beta lactamase-producing-ampicillin-resistant strains of *H. influenzae*, there is evidence of increased resistance to cefaclor and amoxicillin/clavulanate. Again, cefditoren demonstrates activity against *H. influenzae* comparable to that of injectable cephalosporins and levofloxacin (Blasi *et al.*, 2013). Therefore, based on the literature, cefditoren confirms what has been demonstrated by Blasi and colleagues (*Figure 1*):
   – broad spectrum of activity extended to the most commonly isolated pathogens in AECB;
   – a high intrinsic potency (MIC_{90}) which is able to overcome resistance to antibiotics widely used in the therapy of respiratory infections;
   – optimal values of MIC_{50} and MIC_{90} so far.

The most important characteristic of an antibiotic is adequate tissue distribution, i.e., concentrations to ensure therapeutic efficacy at the site of infection. All oral cephalosporins, especially cefditoren, have good penetration into respiratory parenchyma. As shown in *Figure 2*, after a single dose of cefditoren (400 mg), its concentration in epithelial lining fluid (ELF) and bronchial mucosa were still therapeutically relevant, with a tissue-to-plasma concentration rations at 4 hours of 0.545 and 0.318, respectively (Di Marco *et al.*, 2014; Wellington *et al.*, 2004).

Table 2 - *Oral beta-lactams at standard posologies: duration of blood concentration time (%) above MIC_{90} (T> MIC) (Blasi et al., 2010; Blaisi et al., 2013).*

	Posology	S.pneumoniae			H. influenzae		M. catarrhalis
		Pen S	Pen I	Pen R	β-	β+	
Amoxicillin/clavulanic acid	875/125 mg BID/TID	100	40-50	15	40-50	40-50	40-50
Cefuroxima axetil	500 mg BID	80	20	0	50	40	40
Cefixima	400 mg OD	60	0	0	96	96	50
Ceftibulen	400 mg OD	70	0	0	50	50	70
Cefpodoxima proxetil	200 mg BID	100	25	0	50	50	60
Cefditoren pivoxil	200 mg BID	90	54	33	90	90	80
	400 mg BID	---	---	45	---	---	---

Legend: β- - beta-lactamase negative; β+ - beta-lactamase positive; BID – two times a day; I – Intermediate; OD – once a day; Pen – Penicillin; R – Resistant; S – Sensitive; TID – three times a day.

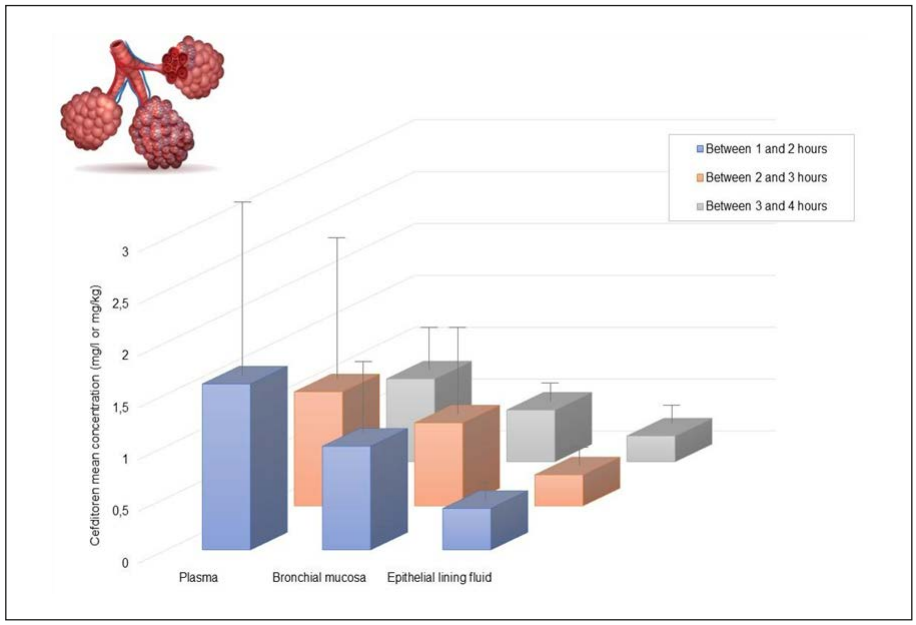

***Figure 2** - Diffusion of ceftditoren in respiratory tissues after a single 400 mg dose of cefditoren pivoxil (Di Marco et al., 2014; Wellington et al. 2004).*

V. Cefditoren in the treatment of uncomplicated skin and skin-structure infections

Skin and soft tissue infections (SSTIs) are bacterial infections of skin, subcutaneous cellular tissue, deep fascia, and muscle (Silverberg *et al*., 2021). Cabañero Navalón *et al.* carried out a literature review on the current role of cefditoren in the management of community-acquired SSTI, showing that this oral cephalosporin is a good choice in the treatment of uncomplicated infections and also that it can be used for an antimicrobial therapy switch to an oral agent in complicated SSTIs (Cabañero Navalón *et al.,* 2021). Gram-positive aerobic cocci, in particular *S. aureu*s and *S. pyogenes*, are the microorganisms most frequently involved in the pathogenesis of SSTIs, followed by *Streptococcus* groups B, C, and G, *Enterobacterales*, *P. aeruginosa*, and anaerobes (*Bacteroides fragilis* group and *C. perfringens)*. As pointed out above, cefditoren has an extended spectrum of activity against gram-negative, gram-positive and some anaerobic microorganisms, including those frequently implicated in SSTIs. Even though there is a lack of accepted breakpoints, cefditoren might be a good option for the treatment of SSTIs (Cabañero Navalón *et al.,* 2021) because of excellent activity against MSSA, with MIC_{50} values of 0.25-0.50 mg/L and MIC_{90} of 0.5 to 1 mg/L (Tempera *et al.,* 2010; Biedenbach *et al.,* 2009) and 100% sensitivity rates of *S. pyogenes*, regardless of macrolides and lincosamides resistance, with MIC_{90} ranging from 0.03 mg/L to 0.06 mg/L for cefditoren. In two multicentre randomised trials, Bucko *et al.* compared cefditoren (200 or 400 mg) with cefuroxime (250 mg) or cefadroxil (500 mg) for the treatment of SSSIs, including those caused by *S. aureus* and *S. pyogenes*. They found that the efficacy, the microbiological eradication rate, and the tolerability (≤5% discontinuation for adverse events) were similar for the three molecules (Bucko *et al.,* 2002).

VI. Intravenous to oral therapy switch

There are multiple advantages in switching from intravenous to oral therapy: reduction of antimicrobial treatment costs, reduced need for accessories and devices for the preparation and administration of the drug (i.e., needles, infusion sets, syringes, intravenous solutions), greater comfort, mobility, and independence for patients, and reduction of complications and adverse effects related to intravenous administration, such as infections of venous access (i.e., phlebitis and thrombosis) and nosocomial infections, and reducing hospital stay (Cobos-Trigueros *et al.,* 2016; Candel *et al.,* 2016).

a. Acute pyelonephritis

The overall duration of treatment for acute pyelonephritis is generally 5 to 10 days, depending on clinical response (symptomatic improvement within the first 48 to 72 hours of therapy) and chosen antimicrobial: fluoroquinolones are generally administered for 5 to 7 days, trimethoprim-sulfamethoxazole and beta-lactams 7 to 10 days (Hooton, 2012). In a prospective, randomised, double dummy, placebo-controlled trial, Monmaturapoj *et al.* demonstrated that IV ceftriaxone followed by oral cefditoren pivoxil is highly effective and well-tolerated for the treatment of acute pyelonephritis, even for uropathogens with a high proportion of quinolone-resistant strains (Monmaturapoj *et al.,* 2012). Beta-lactam antibiotics such as third-generation cephalosporins have been advocated as quinolone-sparing agents, and intravenous

cephalosporin in monotherapy (ceftriaxone) in hospitalised patients is considered a standard treatment. Cefditoren pivoxil might have a role in patients with acute pyelonephritis who meet criteria for switch to oral therapy (improvement of signs and symptoms of infection, absence of fever, normalisation of laboratory exams) because of high volume of distribution and primary excretion of unchanged drug through the urinary tract of approximately 20% to 30% (Sádaba *et al.,* 2007). At the dose of 400 mg once daily, it has excellent bactericidal activity against certain Gram-positive and Gram-negative pathogens which are common aetiologic agents of urinary tract infections. Indeed, it has excellent *in vitro* activity against non ESBL-*E. coli*, non ESBL- *Klebsiella pneumoniae*, and non ampicillinase C (AmpC)-*Proteus mirabilis*. Some studies have shown that the activity of cefditoren against *Enterobacterales* involved in community-acquired urinary tract infection is superior to that of ciprofloxacin and cefuroxime and similar to that of fosfomycin (Monmaturapoj *et al.,* 2012).

b. Lower respiratory tract infections

Before switching to oral formulation, some clinical criteria have to be considered: heart rate 90 mmHg, oxygen saturation >90%, good level of consciousness and tolerance to the oral route (Ramos Lazaro *et al.,* 2021). The selection of the appropriate oral antimicrobial should be done in the same way as the intravenous: possible expected aetiology (causative microorganism), local sensitivity and resistance patterns, PK/PD characteristics of each antibiotic and epidemiological situations and, certainly, characteristics of the patient (for example: age, comorbidity, contraindications, allergic history) (*Table 3*) (Cantòn *et al.,* 2022). In case of third-generation intravenous cephalosporins, the most appropriate sequential therapy is cefditoren due to the fact that it has a similar spectrum and intrinsic activity with ceftriaxone/cefotaxime (Cantòn *et al.,* 2022; Menéndez *et al.,* 2019).

VII. The potential role of cefditoren in combination with other beta-lactams in the treatment of enterococcal infections

Six PBPs (PBP1, PBP2, PBP3, PBP4, PBP5, PBP6) are generally expressed in enterococci (Fontana *et al.,* 1980). The standard of care for severe enterococcal infection (such as endocarditis) is penicillin or ampicillin combined with an aminoglycoside to generate bactericidal activity. The combination of ampicillin and ceftriaxone represents a newer regime with clinical cure rates equivalent to that of ampicillin plus gentamicin for *E. faecalis* endocarditis regardless of whether the isolate expresses high-level aminoglycoside resistance (Fernandez-Hidalgo *et al.,* 2013; Suzuki H *et al.,* 2020) and with lower toxicity (Baddour *et al.,* 2015). The synergy between these two compounds might be due to partial saturation of PBP3, PBP4, and PBP5 by ampicillin and total saturation of PBP2 and PBP3 by ceftriaxone (Fontana *et al.,* 1980, Mainardi *et al.*, 1995; Gavaldà *et al.,* 1999). Similar to ceftriaxone, cefditoren might have the ability to bind to enterococcal PBPs. Indeed, *S. pneumoniae* PBP2X, one of the targets of cefditoren, has affinities with PBP4 of *E. faecalis*: this might explain a certain activity of cefditoren against *E. faecalis* (Moon *et al.,* 2018; Attanasio *et al*., 2020). The combination of amoxicillin (which is basically the oral form of ampicillin and partially saturates enterococcal PBP3, PBP4, and PBP5 alike) and cefditoren in the treatment of *E. faecalis* endocarditis has been investigated by Attanasio and colleagues (Attanasio *et al.,* 2020): for the first time, five patients with *E. faecalis* endocarditis underwent partial oral endocarditis treatment with the combination of amoxicillin/clavulanate acid plus cefditoren. These five patients (all of whom fitted Duke's criteria for the diagnosis of definite endocarditis and none of whom had undergone cardiac surgery) were initially treated with intravenous therapy with amoxicillin/clavulanate 2.2 g every 8 h and ceftriaxone 2 g every 12 h; after a median time of 28 days they were switched to oral with amoxicillin/clavulanate 1 g every 8h and cefditoren 400 mg every 12 h for about 120 days. Clinical and microbiological cure were achieved, and two patients presented a positive PET-CT at the end of the follow-up period without infection recurrence (Attanasio *et al.,* 2020). Further studies are needed to confirm a possible role of cefditoren in the treatment of enterococcal endocarditis.

Table 3 - *Equivalence of antimicrobial for sequential therapy in patients with COPD exacerbation or CAP (Canton et al. 2022).*

Intravenous treatment	*Oral treatment*
Amoxicillin-clavulanic acid	Amoxicillin-clavulanic acid or cefditoren
Fluoroquinolones	Fluoroquinolones
Macrolides	Macrolides
Cefotaxime or ceftriaxone	Cefditoren

CONCLUSIONS

Cefditoren pivoxil is an oral third-generation cephalosporin with activity against *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis,* and non ESBL-, non-AmpC-, non carbapenemase-producing *Enterobacteriales*. It is approved for the treatment of upper and lower respiratory tract infections and skin and skin structure infections. Beyond the authorised indications, a potential role of the drug in combination with other beta-lactams for the partial oral treatment of difficult-to-treat infections such as infective endocarditis deserves further consideration.

Authors' contribution

SG: review design and manuscript preparation; AA, LM: literature review and manuscript preparation; FS: editing and manuscript preparation; CT: review design, literature review and manuscript preparation.
All authors read and approved the final version of the manuscript.

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